DETAILED ACTION

Claims 1, 3-25, 31-33 and 36-38 are pending.

Claims 6-11, 13-25, 31-33 and 36-38 are withdrawn from examination as detailed below.

Claims 1, 3-5 and 12 are examined on the merits.

Please noted that the Examine handling this application has changed and is now Stephen Kapushoc in Art Unit 1634. Please address any future correspondence regarding this application to the above named Examiner.

Election/Restrictions

1. Applicant's election without traverse of the invention of Group I (methods for diagnosing predisposition to chromosomal abnormalities associated with Down's Syndrome) in the reply filed on 08/18/2010 is acknowledged. Applicants furhter Election of the subject matter relevant to detecting mitochondrial deletions (part (a) of claim 1) and analysis prior to conception (claim 5) is also noted. It is noted that applicants also elected the species related to claims 8 an 9, however as discussed in the interview of 09/20/2010 (see accompanying Interview Summary), such an elected is not consonant with the election of part (a) of claim 1.

2. Claims 6 and 7 (as they require non-elected 'after conception'), 8-11 (as they require non-elected 'membrane potential'), 13-25, 31-33 and 36-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/18/2010.

Claim Objections

3. Claim 12 is objected to because of the following informalities:

The claim recites "a mitochondrial deletion associated with altered metabolic activity wherein said level of mitochondrial membrane potential that is less than a normal baseline value of mitochondrial membrane potential is predictive of said pre-disposition wherein the mitochondrial deletion is a deletion in complex I genes of mitochondrial DNA", where the phrase "wherein a mitochondrial deletion in complex I genes of the mitochondrial DNA is detected" is appropriate and consonant with Applicants' election. Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 3-5 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-5 and 12 are unclear over the recitation in claim 1, from which claims 305 and 12 depend, of the intended use of the method as 'a diagnostic method', however the only method step of claim 1 is 'assessing mitochondrial status in a maternal sample'. While the claim 1 further recites, as consonant with the election, that 'a mitochondrial deletion associated with altered metabolic activity … is predictive of a pre-disposition to a chromosomal abnormality associated with Down Syndrome in a

fetus', this recitation is in a 'wherein clause' that appears to state only an asserted association between a deletion and an abnormality. The recitation in the 'wherein clause' is not recited as a method step require any particular detection, nor is there any step require association of a detected deletion with a predisposition to an abnormality, as would be expected in a diagnostic method. As such there is not a clear nexus between the required method step and the intended purpose of the claimed method. The claims may be made clearer if, for example, claim 1 were to recite:

> A method for identifying a genetic pre-disposition to Down's Syndrome, said method comprising:
> detecting in a maternal sample the presence of a deletion in the mitochondrial DNA, wherein said deletion is associated with altered metabolic activity; and
> correlating the presence of said deletion with a genetic pre-disposition to Down's Syndrome.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arbuzova et al (2002) in view of Schon et al (2000).

Arbuzova et al (2002) teaches that mitochondrial dysfunction results in oxidative stress from altered metabolic activity (e.g. p.681 - Summary), and that the level of reactive oxygen species is increased in Down's Syndrome (DS) cells

and impaired mitochondrial function, indicated by reduced mitochondrial redox activity and membrane potential, is present in DS cells (e.g. p.681, right col.). The reference summarizes that mitochondrial mutations, particularly deletions, have a role in the pathogenesis of DS including chromosomal non-disjunction (e.g. p.682- mtDNA mutations in the pathogenesis and aetiology of DS).

Schon et al further teaches an association between the accumulation of mitochondrial mutations and errors in meiosis that may result in trisomies such as are found in DS (e.g.: p.160 - Abstract; p.165 - Hypothesis; p.168 - Predictions of the hypothesis).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Arbuzova et al (2002) in view of Schon et al, that mitochondrial deletions are associated with DS related trisomy, to perform a diagnostic analysis of a maternal sample to assess predisposition to DS in a fetus. Diagnostic analysis to assess fetal pathology risk was well known in the art at the time the invention was made, and the teachings of Arbuzova et al (2002) include that mtDNA is almost entirely maternal in origin (p.683 – left col.). As such the skilled artisan would be motivated to perform an analysis of maternal mtDNA as the skilled artisan would recognize that such an analysis would provide an alternative method to assess the risk that a mother may produce a fetus with DS. Such an analysis made prior to conception (claim 5) would allow for the skilled artisan to provide genetic counseling to a potential mother. With regard to the limitations of claims 3 and 4, the analysis of samples

isolated (claim 4) from blood (claim 3) was well known in the art, and the skilled artisan would recognize an isolated blood sample as a plentiful source of mtDNA.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arbuzova et al (2002) in view of Schon et al (2000) as applied to claims 1 and 3-5 above, and further in view of Arbuzova (1998).

The teachings of Arbuzova et al (2002) in view of Schon et al are applied to claim 12 as they were previously applied to claims 1 and 3-5.

Arbuzova et al (2002) in view of Schon et al does not specifically provide for a deletion in complex I genes of mitochondrial DNA.

Arbuzova (1998) specifically teaches the presence of mutations in complex I genes (i.e.: ND-1 and ND-5) in subjects with trisomy 21 (e.g. p.129, left col).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of Arbuzova (1998) that complex I gene mutations are found in cases of trisomy, with the teachings of Arbuzova et al (2002) in view of Schon et al, that mitochondrial gene deletions may result in metabolic activity alterations that produce chromosomal abnormalities) to perform a diagnostic assay wherein complex I gene deletions are indicative of a predisposition to DS related abnormalities. The skilled artisan would recognize that the teachings of Arbuzova (1998) provide that complex I gene alteration can be indicative of DS risk, where the teachings of Arbuzova et

al (2002) provide that gene deletions are deleterious and effect metabolic activity leading to chromosomal abnormalities.

Conclusion

9. No claim is allowed. No claim is free of the prior art

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephen Kapushoc/
Primary Examiner, Art Unit 1634